ABSTRACT

Isotretinoin has unmatched efficacy in the treatment of acne. However, because isotretinoin is a teratogen that can cause profound birth defects, the iPLEDGE program regulates the drug's distribution in the United States. To minimize fetal exposure to isotretinoin, the program requires that female patients capable of becoming pregnant use two forms of contraception or commit to abstinence while using this therapy. This manuscript argues that iPLEDGE should be revised to remove abstinence as an acceptable contraceptive option in the face of evidence that disputes its efficacy. All patients, regardless of reported sexual activity, should be required to use data-proven contraception. Potential benefits of the proposed change (iPLEDGE-R) include reducing the number of isotretinoin pregnancies, increasing patient privacy protection, and standardizing patient care. Further investigation needs to guide additional strategies to achieve the program's public health goal; however, the ethical and pragmatic advantages of iPLEDGE-R merit consideration.

KEY WORDS: Isotretinoin, Accutane, acne, iPLEDGE, REMS, pregnancy, teratogen, abstinence, contraception, birth control, risk management, FDA

iPLEDGE Must Abstain from Abstinence

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The oral retinoid drug isotretinoin is widely regarded by dermatologists as the most effective treatment for severe and recalcitrant acne.[1,2] However, this drug can cause significant and even life-threatening fetal malformations if taken during pregnancy. Documented birth defects include craniofacial, central nervous system, cardiac, thymic, and parathyroid abnormalities.[3]

Consequently, the United States Food and Drug Administration (FDA) strictly regulates isotretinoin through the Risk Evaluation and Mitigation Strategy (REMS) program known as iPLEDGE.[3] Implemented in 2006, this restricted distribution program is designed to ensure that no pregnant patients start the drug and no patients taking isotretinoin become pregnant.[2–4]

With the aim of achieving these admirable goals, the iPLEDGE program has requirements for patients, prescribers, pharmacies, and wholesalers. Among these mandates, all female patients of reproductive potential must agree to undergo monthly pregnancy tests and use two forms of birth control or commit to abstinence for the duration of isotretinoin therapy plus one month before and one month after treatment. Prescribers must also counsel every patient and both parties have to complete online documentation before each 30-day prescription can be dispensed.[3]

The Guide to Best Practices for the iPLEDGE Program explains that any form of birth control, aside from complete abstinence, can fail. The program also acknowledges that one of the most common reasons for isotretinoin pregnancies is that women have sexual intercourse when they had intended, in fact, to be abstinent.[3] Indeed, abstinence has been cited as the second most common contraceptive method among isotretinoin patients who became pregnant (birth control pills combined with condoms was the most common method).[5] There were 218 to 310 reported isotretinoin pregnancies each year between 2011 and 2017, but available data do not specify how many of these cases were due to abstinence failure versus improper contraceptive use.[6]

As the iPLEDGE program's data show, in practice, abstinence fails too. Abstinence is 100-percent effective if implemented perfectly; however, its typical-use effectiveness has never been studied and, consequently, its real-world failure rate is unknown.[7] Nevertheless, studies that have examined the efficacy of abstinence-promotion programs offer some insight. One researcher found that five years after adolescents made virginity pledges, there was no difference in sexual behavior between virginity pledgers and matched nonpledgers. Moreover, pledgers were less likely than nonpledgers to practice safe sex by using either condoms or oral contraception.[8]

These findings do not support the use of abstinence as a reliable contraceptive strategy. However, unlike other forms of contraception, abstinence is permitted as a singular method

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for pregnancy prevention under iPLEDGE.[3] The comparison of the perfect use of abstinence with typical use of other forms of contraception misrepresents the success rate of this pregnancy prevention method and therefore undermines the efficacy of the program. It is irresponsible for iPLEDGE to maintain this policy in the absence of data that substantiates the efficacy of abstinence.

We therefore propose that the iPLEDGE program require all patients capable of becoming pregnant to use a data-validated primary form of contraception, such as a hormonal implant, intrauterine device (IUD), oral contraceptive drug, or one of several other options. These birth control methods all have a typical use effectiveness of 92 percent or higher.[3,9] Commitment to abstinence should not be a valid exemption from this mandate. The requirement to also use an approved secondary barrier contraceptive method, such as a male condom, during intercourse should remain unchanged.

This proposed revision of the iPLEDGE program (iPLEDGE-R) has significant ethical and pragmatic advantages. First, it treats all patients capable of becoming pregnant equally. As the data above demonstrate, everyone in this patient population is at risk for pregnancy regardless of their stated intentions with respect to abstinence. It is therefore appropriate to require that all at-risk patients follow the same protocol to gain access to this teratogenic drug. iPLEDGE-R thus avoids the current program's ethically concerning practice of putting additional burdens on some patients seeking treatment but not on others.

Second, iPLEDGE-R improves privacy protection for patients seeking isotretinoin treatment. Patients aged 15 to 17 years comprise one-quarter of all patients seen for acne.[10] Appropriately, many of these teens visit the dermatologist with a parent. To protect patient confidentiality, the current iPLEDGE program recommends that prescribers interview adolescents privately about their sexual history prior to starting isotretinoin.[3] Even during a confidential conversation, however, a patient might withhold information about her sexual activity from the prescriber because she does not want her parent to learn that she needs birth control or find out that she has been denied access to isotretinoin if she cannot commit to using an acceptable birth control method. However, under iPLEDGE-R, a prescriber would explain to the patient and her parent that all patients who can get pregnant must use birth control while taking isotretinoin. Consequently, the adolescent patient can keep her sexual health private from her parent because the use of primary contraception is not related to her sexual activity.

Moreover, iPLEDGE-R increases the privacy protection for all patients who are insured as dependents, including adolescents and young adults covered by a parent's health insurance plan. The billing and claims processing procedures used in private health insurance render it nearly impossible for dependents to have confidential access to sexual and reproductive health care covered by insurance.[11] Under iPLEDGE-R, a young adult using isotretinoin can cite the program's birth control mandate if her parents question her about contraceptive services she received. This freedom to use health insurance for birth control is important because, since 2010, federal law has required that health insurance plans cover contraception and related services without out-of-pocket costs. Few exemptions from this mandate exist.[12]

Third, iPLEDGE-R simplifies the process of prescribing isotretinoin for dermatologists and other health care providers. The current iPLEDGE program can place prescribers in awkward situations with patients who want to choose abstinence for pregnancy prevention. After counseling a patient and discussing her motives for abstaining from sex, a provider might find it challenging—if not impossible—to accurately and objectively evaluate her actual commitment to abstinence. When a provider does not feel comfortable prescribing isotretinoin for a patient, such a refusal can strain the physician-patient relationship.

iPLEDGE-R simplifies this difficult situation and minimizes the potential for an ethical quandary. If a patient resists the idea of using contraception when she is not sexually active, the dermatologist can explain that she trusts the patient's commitment to abstinence; however, the FDA—a neutral party—created the rule and does not allow providers to make exceptions. If the patient cannot commit to using two forms of contraception, then the drug cannot be prescribed to her. This approach prevents the patient from feeling singled out or distrusted by her dermatologist.

Critics might argue that iPLEDGE-R places an unnecessary burden on abstinent patients. It might be considered inconvenient to use birth control. Like all drugs and medical devices, contraceptives have risks and side effects.[3] Some patients might have concerns about the deep venous thrombosis risk associated with estrogen, an ingredient in some forms of hormonal contraception. However, the absolute risk of thrombosis in a healthy adolescent using estrogen-containing combined oral contraceptive pills is only 0.05% per year.[13] Furthermore, contraceptives that do not contain estrogen, including IUDs and the subdermal implant, are widely available.[14] These contraceptives can be excellent options for patients who have an estrogen contraindication such as a history of migraines with aura or deep vein thrombosis.[15] Although the placement and removal of a subdermal implant or IUD requires the patient to undergo an invasive procedure, these devices are safe and highly effective.[16]

A subset of patients might also have personal or religious objections to using birth control. If a patient feels strongly that she does not want to use any form of contraception, she can choose alternative acne treatments. Similarly, a patient who has a particular objection to hormonal contraception can choose a copper T IUD. This option might appeal to women who are concerned about the association between hormonal contraception and an increased risk of breast and cervical cancer.[17]

Other considerations include male transgender patients who, despite taking testosterone supplements, might still have the ability to become pregnant.[18] While this topic is beyond the scope of this paper, we support the use of the gender-neutral category "patients who can become pregnant" in iPLEDGE-R. This terminology respects the gender identity of every patient and recognizes the need for two forms of contraception for all patients in this group.

Admittedly, the annual rate of iPLEDGE pregnancies is already low. During iPLEDGE Year 5 (March 2010–February 2011), there were 155 (0.12%) iPLEDGE pregnancies out of 129,554 female patients capable of becoming pregnant.[19] More recent data about iPLEDGE pregnancy rates are not readily available. However, any number of isotretinoin-exposed pregnancies greater than zero is too many. iPLEDGE-R does not address all causes of

isotretinoin pregnancies. Nonetheless, it seems obvious that iPLEDGE-R would reduce these numbers in addition to having the ethical advantages described.

Further investigation needs to be done to improve the iPLEDGE program through evidence-based changes. In addition to implementing iPLEDGE-R, research could be done on the effects of promoting long-acting reversible contraceptives (LARCs) among patients taking isotretinoin. These patient-independent birth control methods, including IUDs and the subdermal implant, have been shown to be 22 times more effective than non-LARC methods at preventing pregnancy.[20] Given the superior efficacy of LARCs, an argument can be made for further revising the iPLEDGE contraceptive requirements.

We recognize that iPLEDGE-R will be controversial. The current iPLEDGE program already has many cumbersome restrictions, and further requirements should only be implemented after careful consideration. However, we argue that iPLEDGE-R makes valuable strides toward standardizing patient care while possessing the potential to significantly reduce the number of pregnancies among patients taking isotretinoin. The revisions also increase privacy protection for many adolescents and young adults who take isotretinoin. Policymakers should consider the value of these benefits when updating the iPLEDGE program. In the interim, some dermatologists might consider implementing the suggested requirement in their practices in order to better serve their patients.

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